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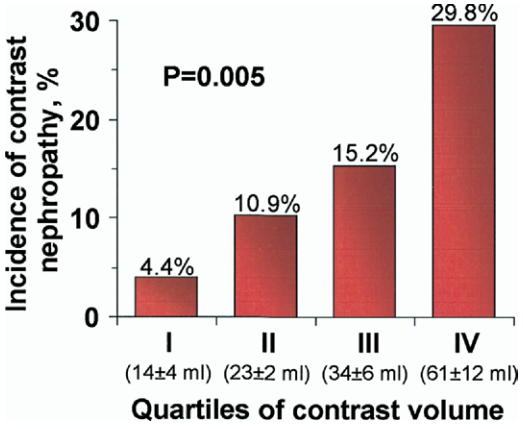

Figure 1 Contrast-Induced Nephropathy

Dose-dependent association of volume of administered contrast with the incidence of contrast-induced nephropathy ($p = 0.005$ by analysis of variance). Mean ± standard deviation of contrast volume for each quartile shown in parentheses.

The major finding of this study is that, as with procedures with higher volumes of iodinated contrast, patients with moderate-severe chronic kidney disease undergoing coronary angiography have an increased, contrast-volume dependent risk of CIN. Despite an elevated risk (1–3) and a high incidence of CIN, ultra-low volumes of contrast were associated with low rates of CIN. These findings have important implications concerning the referral of a patient with moderate-severe chronic kidney disease for diagnostic coronary angiography. With biplane imaging, studies can be performed with very low doses of iodinated contrast (without prolonging procedural times or radiation exposure), suggesting this technique may mitigate the risk of CIN in many patients at highest risk.

Our findings of a very low incidence of CIN with ultra-low doses of contrast are very encouraging, but some limitations of this study need to be considered. Our study was not randomized. While the major factor associated with CIN was contrast volume and the major factor associated with contrast volume was the use of biplane angiography, other factors need to be considered. The use of the iso-osmolar nonionic contrast medium, and that the vast majority received standard therapies of intravenous hydration and N-acetylcysteine likely contributed to a reduction in CIN. While patients had, on average, more than 4 serum creatinine measurements in the week after angiography, we cannot exclude the possibility that the peak measurement in some patients was not identified and hence the overall incidence of CIN was underestimated.

The current findings support the use of ultra-low-dose iodinated contrast facilitated by biplane angiography in patients at increased risk for contrast nephropathy referred for coronary angiography. Further studies will be required to assess the impact of low-dose contrast on the incidence of contrast nephropathy.

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Letters to the Editor

Age Predicts Cancer Incidence Better Than Statin-Induced Low-Density Lipoprotein Level

I disagree with the data analysis in the recently published article in the *Journal* suggesting an association between lower statin-induced low-density lipoprotein (LDL) levels and increased incidence of cancer (1). My analysis of the 8 larger and longer trials (>3 years and >1,000 patients) suggests a clear association between increasing age and increased incidence of cancer (Fig. 1) ($r^2 = 0.77$, $p = 0.004$, regression not corrected for study size). Age is a known and biologically plausible risk factor for cancer. Multivariate linear regression resulted in the following model:

$$\text{Yearly cancer incidence} = -1.103 - 0.012 \cdot \text{LDL on treatment} + 0.0614 \cdot \text{age}$$

The overall model was significant with $r^2 = 0.83$ and $p = 0.013$. The multivariate p value for the coefficient of age ($p = 0.055$) was nearly statistically significant and lower than the multivar-

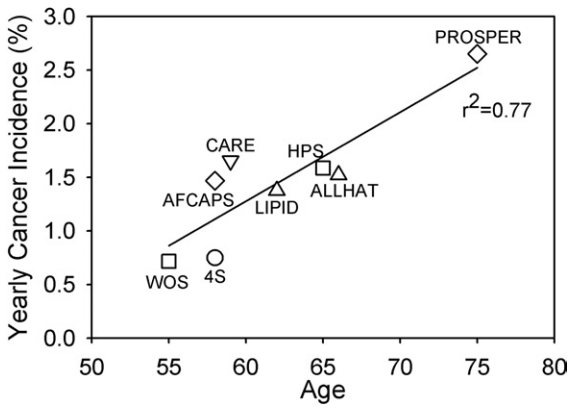

Figure 1 **Dependence of Yearly Cancer Incidence on Age in Patients Treated With Statins**

Cancer incidence was calculated from data provided in Alsheikh-Ali et al. (1). AFCAPS = Air Force Texas Coronary Atherosclerosis Prevention Study; ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; CARE = Cardiac Angiography in REnally impaired patients; HPS = Medical Research Council/British Heart Foundation Heart Protection Study; LIPID = Long-Term Intervention With Pravastatin in Ischemic Disease Trial; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; WOS = West of Scotland trial; 4S = Scandinavian Simvastatin Survival Study.

iate p value for the coefficient of LDL on treatment ($p = 0.26$). This model suggests that age is more predictive of cancer incidence than LDL on treatment. Based on this analysis, we should reconsider the assertion that statin-induced lowering of LDL is associated with increased cancer incidence.

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Please note: Dr. Rembold has received honoraria for lectures on dyslipidemia from Kos Pharmaceuticals, Abbott, AstraZeneca, Merck, Schering-Plough, and Pfizer.

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Risk Associated With Statin Treatment

Several prospective, randomized, placebo-controlled trials have established the fundamental preventive role of statins in the treatment of atherosclerotic disease, including coronary artery disease, stroke, and peripheral artery disease. However, in high-risk cohorts of elderly, hypertensive patients and patients with heart failure, low cholesterol portends a poor prognosis (1,2). This controversial association has been ascribed to the role of cholesterol as a marker of incipient risk, which disappears after accounting for the early deaths (3). In their retrospective meta-analysis of statin users in large randomized, controlled trials, Alsheikh-Ali et al. (4) observed an association between statin-induced lowering of low-density lipoprotein and increased risk of cancer, and they concluded that this may offset some of the benefits of statins. Their conclusion of a relationship is most likely spurious and dependent on an association between incipient cancer risk and attainment of low levels of low-density lipoprotein. Unfortunately, they only reported on the statin groups. It would have been helpful if they excluded a similar association among the placebo groups and if they had presented data excluding deaths within the first year after onset of statin treatment, which may be confounders. In the longest follow-up of any statin trial, 4S (Scandinavian Simvastatin Survival Study) demonstrated that after 10 years there was a nonsignificant trend toward less cancer among patients who received simvastatin treatment during the trial period (5).

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Low Low-Density Lipoprotein Cholesterol and Cancer Risk

The central finding in the report by Alsheikh-Ali et al. (1) was Figure 9, which suggested a relationship between achieved low-density lipoprotein (LDL) cholesterol and newly diagnosed cancers in 13 arms of statin trials. I suggest that the relationship is confounded by age in various trials. The authors accounted for sample size, but seemingly not for age, which is a bit surprising, as age-adjustment is one of the most frequent procedures in epidemiologic research. Are there some specific reasons for not doing so? In any case, reasons are not stated.